ON THE MECHANICAL FACTORS WHICH DETERMINE THE OUTPUT OF THE VENTRICLES.

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THE working capacity of a pump is measured by its output. In the heart the output has to undergo large alterations with varying conditions of the body, and its measurement is therefore the most important quantitative determination connected with this organ. Most of the previous researches on this subject have been carried out on the whole animal, and in view of the difficulty of controlling the different factors involved under these circumstances it is not surprising that considerable discrepancies exist between the views of different workers as to the relative importance of the various factors involved. Thus whereas Zuntz (1) and his pupils describe great variations in the output associated with exercise, and Krogh (2) has actually measured these variations in man, Yandell Henderson (3), as a result of a number of careful experiments, considers it impossible for the heart to more than double its output under any circumstances, though Krogh finds variations in the output of the left ventricle between 2·8 and 21 litres per minute. It seemed to us that the whole question might be put on a securer basis if investigated on the heart-lung preparation as used in this laboratory, where all the mechanical factors of the circulation are under strict control. The results obtained in this way should give us some idea of the capabilities of the heart as a pump, which might serve to explain the behaviour of this organ in the intact animal. It has been shown lately by Markwalder (4) and one of us that, provided the venous inflow be maintained constant, the output of the left ventricle is within wide limits independent of the arterial resistance, the small falling off in the output with rise of pressure, observed in previous experiments, being fully accounted for by the increased leakage from the aorta through the coronary system of vessels as the arterial pressure rises. Knowlton

and Starling(5) found the output practically constant with varying rates of beat caused by differences of temperature, and this has been confirmed by Markwalder and Starling. On the other hand, the output is immediately increased by raising the venous reservoir or increasing in any way the inflow into the right heart. We must therefore focus our attention on the connection between venous inflow, venous pressure and ventricular output.

At the beginning of ventricular systole the ventricular muscle passes rapidly from a condition of relaxation to one of contraction. The auriculo-ventricular valves close at the very commencement of the ventricular contraction. The contraction of the muscle, or rather the rise of contractile stress, then proceeds for a time isometrically, while the pressure in the ventricle is rising to the pressure in the aorta. When the pressure rises to this point the aortic valves open and the muscle fibres are able to shorten. The pressure, however, continues to rise for a time and then falls, or it may run almost horizontally (the 'plateau'). During the plateau the contraction of the ventricular muscle is more isotonic. The extent to which the contraction differs from pure isotonic contraction will vary according to the height of the arterial resistance and the amount of blood which is being forced out of the ventricle. The more marked the 'plateau,' the more perfect will be the isotonicity[1]. The contraction then ceases and relaxation begins with coincident rapid fall of pressure in the ventricle below that in

[1] In view of the complicated arrangement of the fibres of the mammalian heart, it is impossible to determine definitely the relation between the tension on each strand of muscle fibres or on each muscle fibril and the intracardiac pressure. If the cavity of each ventricle were perfectly spherical the tension on each muscle fibre would be greater the greater the capacity of the sphere, assuming the intracardiac pressure to remain constant. (The total pressure on the whole of the boundary layer of a sphere will vary as its surface and therefore as the square of the radius. While the length of each muscle fibre lying in the circumference of the sphere would vary directly as the radius, the amount of fluid to be forced out by a given shortening of the muscle fibres would vary as the cube of the radius.) Since under normal circumstances the capacity of the heart cavities becomes less during the contraction of the ventricle, a constant tension on the muscle fibres would tend to produce a pressure in the heart cavities which would increase steadily as the emptying proceeded and their capacity became smaller. If this were the case, a plateau, *i.e.* a period of constant pressure in the ventricular cavities, would be associated with a gradually diminishing load off the individual muscle fibres as they contracted, a condition which would be favourable for obtaining the maximum mechanical performance out of the contracting muscle. It may be remembered that under normal conditions in the body, most skeletal muscles contract in this way, since they act at a greater mechanical advantage or smaller mechanical disadvantage when contracted than when commencing their contraction. This condition is imitated in Fick's cosine lever. See Burdon Sanderson's article in *Schäfer's Textbook of Physiology*, II. p. 355.

the aorta, which causes a closure of the aortic valves. From this time forward the relaxation of the ventricular muscle differs in its conditions from the relaxation of a muscle recovering from a muscle twitch. A skeletal muscle has no power to lengthen itself actively,—it has to be lengthened by the application of some extending force. It presents, however, little resistance to extension, so the extending force may be very small. On the other hand, the contractile state does not disappear instantaneously, so that the curve of lengthening of a muscle alters with variations in the extending weight, the lengthening period being shortened by increase of the weight on the muscle. In the same way, in order that the ventricular muscle may lengthen, the ventricles have to be distended by the inflow of fluid, though the pressure necessary to distend them is almost negligible. But whereas in the case of the skeletal muscle (under ordinary experimental conditions) the tension exerted by the extending force is the only factor of importance, in the heart the rate of application of the extending force, *i.e.* the rate of inflow of the blood, is still more important than the tension exerted by it on the walls of the ventricle. The ventricles cannot dilate unless fluid enters them, so that they may be, so to speak, 'after-loaded' at every stage of their relaxation. If blood therefore does not enter the heart, the ventricles do not dilate at all during diastole and may become smaller and smaller with each systole until they are empty. This condition has been described by Henderson, as the result of acapnia, as 'increased tonicity of the heart,' but it is purely a mechanical result of absent or deficient venous inflow. An 'adequate' venous inflow might therefore be defined as one which is exercising a minimal distending force on the ventricular muscle throughout the whole of its relaxation, so that at no time can the muscle be regarded as after-loaded. Under these circumstances, if the diastole be prolonged, the heart will dilate to its maximum or until restrained by the surrounding pericardium. As a rule, however, before this condition of extreme dilatation is attained, a new systole begins, the auricle empties itself into the ventricle, and then the ventricle contracts once again. If the venous inflow is still greater, *i.e.* more than adequate, it may exert an active tension on the ventricular muscle during its period of recovery from the contracted condition and during the whole of its subsequent relaxed condition. In this case the important factor is now the pressure at which the blood enters the auricles and ventricles. The higher the pressure the more rapidly it will stretch these structures, and the more rapid therefore will be the acquisition by the heart of its maximal condition of dilatation.

In view of these facts it is difficult to see how it is possible to maintain Henderson's dictum that the curve of filling of the heart is the same under all circumstances. The rate of filling must depend first on the rate at which the blood enters the heart from the veins, and secondly on the pressure at which the blood enters the heart. It will therefore be necessary to enquire into the influence of the variations of the venous pressure and venous inflow on the diastolic filling and the output of the ventricles. (The question of the volume curve will be dealt with in a subsequent paper.)

In dealing with variations of venous pressure, *i.e.* the pressure in the big veins at their entry into the auricles, it is important to remember that this may be altered under two conditions. In the first place with a moderate inflow, *i.e.* any amount up to what we have defined as adequate, variations in the rate of inflow of blood will first cause very little change of pressure, the increasing inflow being merely sufficient to relieve the after-loading of the ventricular muscle during its relaxation. As soon as the inflow exceeds the rate at which it can keep pace with the relaxation of the ventricular muscle, the pressure at the auricular orifice of the great veins must begin to rise, and this pressure will exert an active distending influence on the ventricular walls, so still further quickening the rate of filling of their cavities and increasing the output from the ventricles. On the other hand the venous flow must be maintained by means of a reservoir which is some distance above the level of the heart. If for any reason the heart fails in its pumping action, the blood will remain in the auricles and ventricles and will prevent the further entry of blood from the reservoir. The heart will dilate more and more after each inefficient systole, while the pressure in the great veins will rise steadily: but this rise of pressure will be associated not with increased output from the ventricles but with diminished output. We have therefore to distinguish between a rise of venous pressure which is effective in dilating the heart during diastole and increasing its output, and a rise of venous pressure which is passively induced by failure of the pumping action of the heart.

Under normal conditions, *i.e.* with a heart working under a load which it can easily accomplish, the pulmonary circulation introduces no complications. Commencing failure of the heart may, however, be marked either on the right or left side, and we shall have later to consider how the circulatory conditions in the lungs affect and are affected by the conditions in the systemic circulation.

In our experimental investigation of these points we have been met by several difficulties and experimental limitations, the existence of which in our early experiments we did not suspect. The first was due to our failure to appreciate the viscosity of the blood and the influence of this factor on its flow through tubes. We found that, in consequence of this viscosity, our venous reservoir with its system of fairly wide tubes was only delivering fluid at the rate of a few 100 c.c. per minute into the heart, and that the maximum output of the heart was really limited by the amount which would flow from our venous reservoir. It seemed easy to get over this by putting the venous reservoir higher and connecting it by a long tube with a cannula in the superior vena cava. This gave a larger inflow but had the disadvantage that if for a short time the action of the heart failed, the blood accumulated in the right heart at an enormous pressure which caused damage to the heart wall, or if the right heart responded fairly well, might cause pulmonary œdema. The same drawback attended our efforts to increase the flow into the right heart by exerting pressure upon the blood in the venous reservoir by blowing air into this vessel. These difficulties were finally obviated by using a large reservoir a short distance above the heart and connecting it with the venous cannula by a short piece of hose pipe, the rate of blood flow being regulated by a screw clip on the hose pipe. We met with the same type of difficulty on the arterial side of the system when attempting to determine the maximum output the heart was capable of. All our tubes were found to be too narrow, so that finally we had to insert a wide cannula of the diameter of the aorta directly into the arch of the aorta and connect this by a wide rubber tube with the arterial resistance, replacing all the tubes throughout the system by tubes of the same diameter. Under these circumstances the heart was working at what appeared to be its maximum capacity and maintained a pressure at the beginning of the arterial system of 100 mm. Hg. without any resistance in the system at all, other than that offered by the flow of blood through the wide tubes.

Anatomically the vascular system may be compared, so far as its total cross section is concerned, to a double cone widening continuously from the aorta to the capillaries and narrowing again to the venæ cavæ. The tubes representing the aorta and vena cava in any artificial schema should therefore be the narrowest parts of the circulation. Under conditions of rest, however, we should have to represent the general tonic constriction of the arterioles by a number of stopcocks placed on the arterial side of the capillaries, impeding the escape of blood from the

arterial system and so maintaining a normal arterial pressure. Under conditions of stress, when there is a maximal inflow and output, in our schema most of these stopcocks would have to be open, and in the animal there must be dilatation of the arterioles over so considerable an area that it becomes difficult to speak of a 'peripheral' resistance, the resistance of the whole system being no greater than if it consisted of a single tube with a diameter throughout about equal to the aorta. The work of the heart under these conditions is thus spent on driving the viscous blood at a great velocity through a comparatively wide system of tubes.

Finally it must be remembered that in one respect it is impossible to reproduce the conditions in the intact animal on our heart-lung preparation. In the intact animal the heart and lungs are normally under a negative pressure which, amounting only to a few mm. Hg. under normal circumstances, may increase to as much as 30 mm. Hg. during forced inspiration. When the heart is passive, as during diastole, this negative pressure will act on its walls and on the intra-thoracic portion of the great veins. During inspiration the descent of the diaphragm causes a positive pressure in the abdomen, so that the venous blood as it passes from the abdomen to the thorax passes into a great trough of pressure. If the negative pressure in the thorax is 30 cm. of water and the blood enters the thorax at such a rate as to maintain the pressure in the great veins at zero, *i.e.* equal to atmospheric pressure, the distending force on the auriculo-ventricular walls may be taken at 30 cm. of water. In our heart-lung preparation we could therefore only imitate this condition by passing in blood at such a rate that it exercised a positive pressure of 30 cm. of water on the heart walls. In the intact animal this great distending force will be active only during inspiration itself and will be lessened during expiration, though not abolished. In our experiments it must be active throughout the whole experiment. The larger positive pressure which we have to use in our experiments extends also to the vessels as they pass through the lungs, so that the working of a heart-lung preparation at its maximum efficiency is more dangerous for the lung vessels than it would be in the intact animal, and if persisted in too long tends to give rise to pulmonary œdema. It is possible to enclose the heart in a glass vessel and to expose it to a negative pressure of any desired extent, but we cannot conveniently devise a similar method of relieving the internal pressure on the lung vessels. But it is evident that the venous pressures we are warranted in adopting in our experiments in testing

the maximum functional efficiency of the heart, must be much higher than the positive pressures observed in the big veins of the intact animal. In the latter circumstances 5 cm. positive pressure in the big veins might be equivalent to a positive pressure of 35 cm. of water in the heart-lung preparation.

Methods. All the experiments which form the subject of this article were carried out on dogs varying from 4 to 6 kilos. in weight. The heart-lung preparation was made as already described, the main difference in the apparatus employed in our experiments was in the

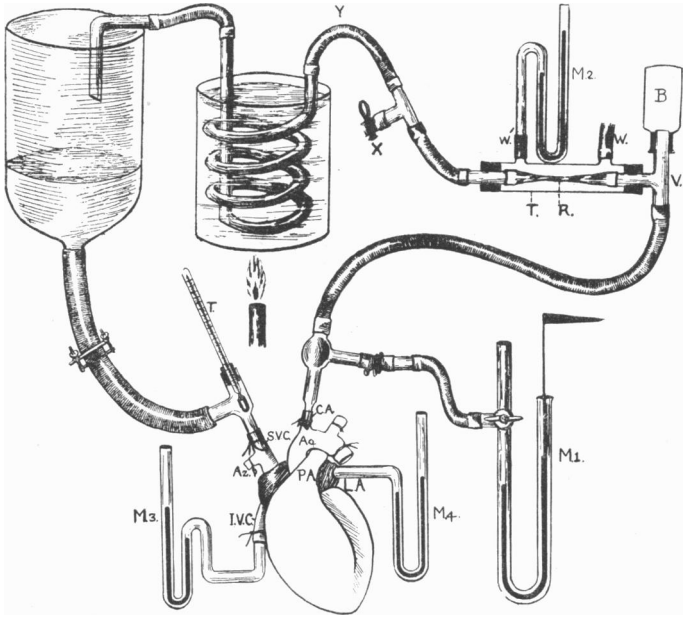

Fig. 1.

size of the tubes employed. The arterial cannula had a bore of 8 mm. and was connected with the artificial resistance by a rubber tube with an internal bore of 8 mm. diameter. From the venous side of the resistance a rubber tube of similar bore passed to a glass spiral immersed in warm water kept at a constant temperature by means of a gas burner. On the connecting tube was a T-piece which could be opened so as to allow the whole blood coming through the arteries to flow out into a graduated vessel (Fig. 1). The time of filling of the vessel was taken by means of a stop-watch, thus giving the output of the left ventricle. From the glass spiral a tube led the blood into an inverted

bell jar, from the bottom of which passed a rubber tube with an internal bore of 12 mm. to the venous cannula. The venous cannula in each case was chosen of the maximum size which could be inserted into the superior cava. When it was desired to determine the maximum output of the heart a still larger arterial cannula was used and was inserted directly into the arch of the aorta. The pressure in the inferior cava at its opening into the right auricle was measured by means of a long wide tube filled with hirudin solution, which was passed up from an opening in the inferior cava in the abdomen and tied in the inferior cava in the chest, so that its orifice lay close to the right auricle. This was connected with a water manometer. To the upper end of the water manometer a tube led to a piston recorder which served to show qualitatively differences in the venous pressure. In each case the piston recorder readings were controlled by a direct reading of the height of the fluid in the water manometer. The pressure in the left auricle was measured by inserting a cannula filled with hirudin solution into the left auricle through the left auricular appendage. It was secured by a ligature round the appendage. This also was connected with another water manometer, the excursions of which were registered by means of another piston recorder. A screw clip was placed on the tube passing from the venous reservoir to the superior cava, so that the inflow of the blood could be regulated to any desired extent. The height of the venous reservoir above the inferior cava was 35 cm. This was therefore the maximum pressure which could be brought about in the superior cava or right auricle, apart from very sudden rises of pressure due to contractions of the ventricle with incompetent auriculo-ventricular valves.

1. *The connection between venous inflow, ventricular output and venous pressure.*

The connection between these three quantities was investigated in various ways. In some cases the arterial pressure was kept absolutely constant by adjusting the air pressure round the arterial resistance so as to maintain the mean aortic pressure, as recorded on the kymograph, level. In most cases, however, the artificial resistance was maintained at a constant height, as judged by the height of the mercurial manometer connected with the air space outside the thin rubber tube which formed the resistance. Under these conditions, increased inflow and output of the heart caused an increased pressure in the aorta, since more fluid had to be passed in a given time through the artificial

resistance. The rise of pressure was as a rule less than 30 mm. Hg., and in view of the constancy of the output of the left ventricle under varying arterial resistance, which has been shown in the paper by Markwalder and Starling, it seemed hardly necessary to trouble about an absolute adjustment of the mean aortic pressure.

The effect of altering the inflow was observed in various ways. In the earlier experiments the inflow was modified by altering the height of the venous reservoir. In the later experiments with larger tubes, the inflow was raised in steps from a minimal to a maximal amount by unscrewing the clip on the tube passing from the venous reservoir to the vena cava. So long as the heart continues to beat and maintain a circulation, its output must be equal to the venous inflow, and may be used therefore as a measurement of the latter. It is evident that the heart could not continue to throw out more blood than it received, and if it threw out less blood, each beat would leave the heart fuller than before, so that in a very short time the heart would be over distended and the circulation would come to an end. The results of four such experiments are given in the following tables.

TABLE I.

EXP. 1. Heart 84 gms. Small cannulæ in innominate artery and inferior vena cava.

Arterial B.P.	Pulse rate per min.	Height of venous reservoir (cms.)	Output per minute (c.c.)	Pressure I. V. C.
112	162	5	300	56
116	162	8	420	55
124	162	18	483	57
128	162	24	600	58
138	162	35	714	64
146	162	42	732	68
140	156	33	618	60
126	156	24	498	55
116	150	14·5	428	51
110	150	11	318	48
110	150	8	246	47
20	156	5	216	32
36	156	17	445	46
60	156	27	600	50
80	156	36	696	54
50	156	23	558	45
36	156	13	375	38
24	150	7	234	30
164	168	6	130	60
170	168	13	240	70
174	168	22	333	105
184	168	28	374	125
184	168	33	428	150
182	168	24	384	115
178	168	20	352	92
172	168	10	196	66

Exp. 2. Dog 6·45 kilos. Heart 44 gms. Cannulæ in aorta and inferior vena cava; cardiometer.

Temperature	Arterial B.P.	Pulse rate per min.	Pressure I. V. C.	Output per minute (c.c.)	Output per beat (c.c.)	Venous supply
36°	80	144	12	215	1·49	small
	92	144	32	850	6·00	+
	112	144	80	2000	13·90	+
	110	125	34	1620	12·00	–
	90	125	5	800	5·90	–
34°	80	120	0	105	0·87	small
	98	129	36	1070	8·30	+
	112	138	76	1580	11·40	+
35·3°	112	144	130	2000	13·90	+
	112	144	86	1620	11·20	–
	98	144	30	1000	6·95	–
36°	84	150	12	260	1·70	–

Exp. 3. Dog 5·15 kilos. Heart 56 gms. Cannulæ in innominate and inferior vena cava.

34·5°	100	126	20	560	4·2	small
	110	126	60	1100	8·7	+
	110	129	100	1500	11·6	+
	96	132	150	1720	13·0	+
	90	132	230	2400	18·2	+
	90	135	250	3000	22·3	full

Exp. 4. Dog 5·75 kilos. Heart 52 gms. Cannulæ in aorta and inferior vena cava. Cardiometer.

30°	72	92	12	270	2·72	small
	80	92	46	732	7·40	+
29·5°	84	92	74	1400	14·10	+
30°	90	114	94	1710	15·00	+
30·5°	86	114	46	1316	11·70	–
36·3°	70	162	20	666	4·10	small
36·2°	84	162	58	1316	8·40	+
	88	162	56	1670	10·30	+
35·5°	60	150	0	150	1·00	–

In the first of these the venous inflow was increased by raising the venous reservoir, in all the others by alteration of the clip on the wide tube used to connect the reservoir with a wide cannula in the superior vena cava, the level of the blood in the venous reservoir being about 35 cms. above the heart. These experiments show clearly that the output of any heart can be varied within wide limits by alteration of the venous inflow, and that within these limits it varies directly as the venous inflow. So long as the functional condition of the heart remains constant, the amount put out at each beat depends directly on the

diastolic filling. If we are to understand the factors responsible for the power of the heart to adapt its output to the inflow, it is necessary to study the relation of the pressures on the venous side of the heart to the volume of inflow. This relation is shown in the curves (Fig. 2) in which the venous pressures in nine different experiments, as measured on the right side of the heart, are plotted against the output. It will be seen that as the inflow and output gradually increase, there is a slight rise of venous pressure with each increase. The height

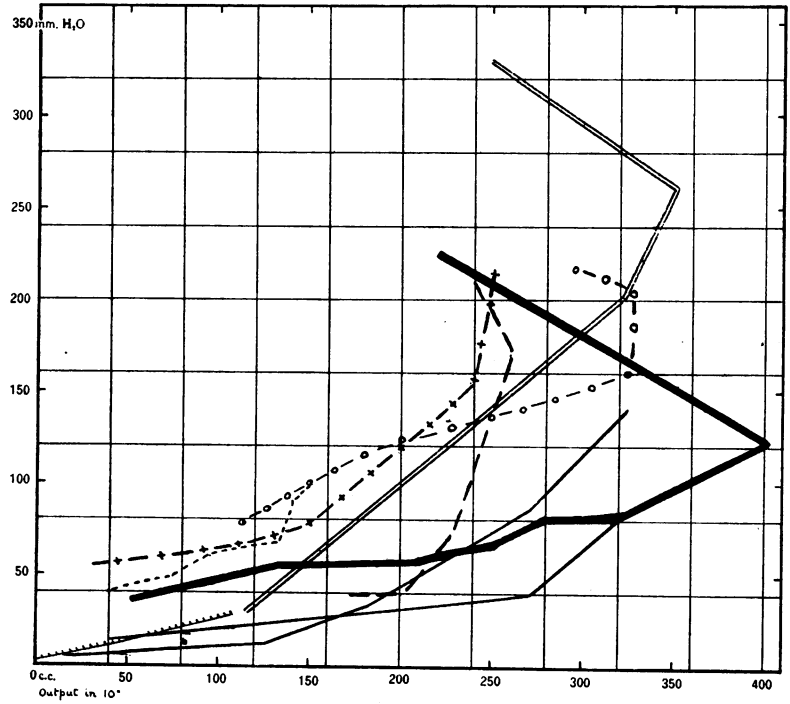

Fig. 2.

of the venous pressure does not, however, rise in a straight line but in a curve, becoming more rapid as the limits of the functional capacity of the heart are reached, until in some cases the heart becomes over distended, is unable to deal with the blood filling its cavities, and the output diminishes, although the venous pressure rises to a maximum. During the first part of the curve, with small to moderate output, we may say that the venous pressure, as measured at the entry of the vena cava into the right auricle, is mainly important in providing a quick flow of blood into the right auricle and

ventricle, so as to maintain a slight distending force on the relaxing ventricle, so that the blood is always present to follow the ventricular wall as it relaxes. As the inflow increases still further, the pressure begins to rise more rapidly and now becomes an effective factor in distending the ventricular wall and quickening the rate at which lengthening occurs after the end of systole. It is evident that there must be some limit to the process by which rise of venous pressure causes increased filling and increased output of the heart. This limit is probably reached when the venous pressure is high enough to produce maximal distension of the heart just as the next systole begins. This explanation, however, at once brings in the further question as to the significance of maximal dilatation. Is the maximum set by the connective tissue framework of the muscular heart wall, or does it vary with the functional capacity of the heart? The fact that with a high arterial resistance the maximum possible output is smaller than with a moderate resistance would at first seem to point to the optimum distension as being dependent on the functional capacity of the heart muscle. We have found, however, that, as the arterial resistance is increased, the amount of residual blood remaining in the ventricle after each systole is also increased, so that, assuming that each heart has a constant of maximum distension set by the length of its muscle fibres and the arrangement of its connective tissue, it will attain this maximum during diastole with increasing venous inflow sooner, if the arterial resistance is high, than when the arterial resistance is low. We are inclined therefore to believe that the maximum capacity of the heart is a fixed quantity for each heart and is dependent on its structural arrangements[1].

[1] The conditions urged in the footnote on p. 358 must also have an important bearing on the question of maximum distensibility of the heart. With increasing distension both cavities of the heart tend to become more spherical, so that whatever be the relations between tension of muscle fibre and intraventricular pressure in the contracted heart, they must tend to approach more nearly those ruling in a sphere the greater the distension of the heart. In the distended heart the tension on each muscle fibre will rise much more rapidly than the intracardiac pressure, and the more distended the heart, the greater will be the mechanical disadvantage under which the muscle fibres act, and this ever-increasing disadvantage must finally result in a condition in which the muscle fibres are unable to contract at all or to raise the intracardiac pressure higher than that existing at the end of diastole. The heart's action must then come to an end. It seems probable that the connective tissue framework of the heart would be so arranged as to limit as far as possible the attainment of this condition. Under normal circumstances it will be prevented by the restraining influence of the fibrous tissue of the pericardium, as was shown by Barnard.

Light is also thrown on the significance of the venous pressure in relation to the output of the heart by the experiments in which the rate of the heart beat was modified by alteration in temperature. In Exp. 4, Table I, the venous pressures were measured with varying inflow, first at about 30° C., and secondly at about 36° C. It will be observed that in the first series at 30° C. the venous pressures are uniformly higher than in the second series at a higher temperature with corresponding outflow. The results of an instructive experiment are also shown in Fig. 2 of Markwalder and Starling's paper. In this experiment the output was maintained constant, while the heart rate was altered by alteration in the temperature. With a moderate inflow the output remained constant between 72 and 156 beats per minute. The venous pressure however rose considerably with diminution in rate, namely from 38 to 110 mm. H_2O. In the second half of the same experiment, with an inflow of about 1250 c.c. of blood, the output also remained constant between 102 and 156 beats per minute. On further slowing the rate of the heart, the total output fell slightly to 1030 c.c. per minute. The rise of venous pressure was still more marked with the higher output. Starting at the highest rate of 156 at about 76 mm. H_2O, it rose to 190 mm. H_2O with a heart rate of 60. It must be remembered that with a constant output per minute, slowing of the heart rate means a proportional increase in the output per beat. In the experiment just quoted, the output per beat varied very considerably. This signifies that at the end of each diastole, the heart must be more distended when beating slowly than when beating more rapidly. To effect this distension a greater pressure is necessary. Since the output remained constant, one cannot speak here of a back pressure, the heart throwing out at each beat as much blood as it received between the beats. The sole significance of the rise of the venous pressure in this case is therefore to produce an increasing distension of the ventricle. It is evident, however, that in this way the heart will attain its maximum distension at a slow rate of beat with a smaller total inflow (*i.e.* inflow per minute) than at a more rapid rate of beat, so that there will be a limit to the degree to which a rise of venous pressure can be advantageous in causing an increased output of the heart. Prolongation of diastole, while not altering the total output of the heart with a moderate inflow, will tend to lower the maximum output per minute of the ventricles. With a constant inflow, increased rate of the heart will not alter the output of the heart. If, however, the venous pressure be maintained constant, increased rate of heart beat will cause increased

output, since, with increasing rate the venous pressure can be maintained constant only by increasing the inflow. It would seem to follow from this argument that the shorter the diastole, and therefore the more rapid the contraction of the heart, the greater will be the maximum output of the ventricles. This is true also in the sense that a higher venous pressure is more effective in increasing the output at a high rate than at a low rate of beat. With shortening of the diastole the venous pressure becomes important in hurrying up the process of lengthening of the muscle fibres, which follows on the completion of systole. The phenomenon of the refractory period shows that the functional state of the cardiac muscle is not a constant quantity during the diastolic period. It is true that the contractile state passes off rapidly, but the disappearance is not an instantaneous one, so that the lengthening of the muscle under any tension would occupy a certain amount of time, which will be shorter the greater the tension. The shorter the diastole therefore, the greater the pressure which will be necessary within the heart cavities in order to obtain a maximum distension of these cavities before the onset of the increased systole. Thus in Exp. 3, with the heart beating rapidly, the output increased steadily as the inflow was increased up to its full amount. At the maximum output the venous pressure was 250 mm. H_2O. At this point this small heart was putting out 3 litres of blood per minute. It is evident that this increase of maximal capacity with increasing rate must have a limit, but the limit is rather physiological than mechanical and is set by processes of fatigue in the heart muscle. Evans has shown the large increase in metabolism of the heart with the increase of rate which attends rise of temperature, and also that the metabolism is increased by raising the mechanical demands on the heart muscle either by increased inflow or increased arterial resistance. As soon as the processes of recovery fail to keep pace with those of activity and the heart commences to show fatigue, its contraction will be less effective and there will be a larger amount of residual blood at the end of each systole. The heart will thus gradually increase in size until it is almost at its maximum distension at the end of systole, and a very small inflow of blood is sufficient to produce a maximal distension. Here then, nothing will be gained by increasing the venous pressure. The only way to save such a heart is to diminish the inflow and allow the heart time to empty itself and time to recuperate after its exertions.

The effect of moderate fatigue is well shown in Exp. 2. In this animal, with a heart of 44 gms., an output of 2000 c.c. per minute was

obtained at the beginning of the experiment with a venous pressure of 80 mm. H_2O against an arterial pressure of 112 mm. Hg. About half an hour later in the same experiment, with the same rate of beat and the same arterial pressure, the same output of 2000 c.c. per minute was only obtained with a venous pressure of 130 mm. H_2O. This experiment shows us what fatigue of the heart means. In the fatigued heart a greater diastolic distension is necessary to produce a given output of blood at each systole than is required in the fresh heart beating at the same rate. This distension can only be produced by increasing the venous pressure. We shall have to return to this point when analysing the changes in the heart at each contraction which are responsible for the adaptive powers of this organ.

2. *The effect on venous pressure and ventricular output of exposing the heart to a negative pressure.*

As might be expected the positive pressures in the big veins near the heart may be kept much lower with a given inflow by exposing the heart to a negative pressure. For this purpose a glass cardiometer was introduced into the pericardium, which was tied tightly round it near the base of the heart. The side tube of the cardiometer was then connected through a mercury or water valve with a filter pump, so that a constant negative pressure in the vessel round the heart of about 10 cms. of water was maintained but which could be varied at will. The effect was to reduce the readings in the venous manometer whether connected with the right or the left side of the heart approximately by the amount of the negative pressure in the vessel surrounding the heart. The results of a few such experiments are given in Table II below, and demonstrate the truth of the statement made previously that a positive pressure of 150 mm. of water in the big veins, under the ordinary conditions of our experiment, is equivalent to a pressure of plus 50 mm. in the big veins and a negative pressure in the thorax of 100 mm., or to a positive pressure of zero in the big veins and a negative pressure in the thorax of 150 mm. of water in the animal with the intact thorax.

3. *The effect of varying the inflow on the pressure in the left auricle.*

In the preceding pages we have spoken of venous pressure and output from the arterial side, as if the heart consisted of only one auricle and ventricle. As a matter of fact in nearly all the protocols cited, the venous pressures were measured in the inferior vena cava, *i.e.* on the

TABLE II. *Effect of negative pressure.*

No. of exp.	Heart weight	Negative pressure	Arterial B.P.	Pressure I. V. C.	Left auricle	Pulse rate per min.	Output per min. (c.c.)
1	30·5	0	90	28—40	—	168	810
		6 mm. Hg	90	−80——64	—	168	810
2	68·5	10 cm. H_2O	92	0—20	20—40	144	720
		0	92	40—50	64—80	144	720
		10 cm. H_2O	92	0—20	10—30	144	720
		0	96	200	200	144	600
		10 cm. H_2O	96	160	100	144	600
3	53·5	6 cm. H_2O	164	140	125	216	240
		0	164	170	200	216	240
4	49·5	14 mm. Hg	100	−35——5	—	174	672
		0	100	40—80	—	174	672
5	106	0	100	20—30	50—65	102	860
		8 cm. H_2O	100	−20——15	20—35	102	860

right side of the heart, while the output was measured from the left ventricle. It is evident that the filling of the right ventricle is alone directly influenced by the diastolic pressure in the right auricle and inferior vena cava, while the filling of the left ventricle must be a function of the diastolic pressure in the left auricle. It is therefore important to find out how far the pressure in the left auricle undergoes changes with altering venous inflow similar to those which we have found to occur on the right side of the heart. We give below records of five experiments, in which the pressures were measured simultaneously in the inferior vena cava and in the left auricle under varying conditions of inflow and systemic arterial resistance.

These results show that, in a heart that is in good condition, as the inflow is increased from a minimal to a moderate amount, the pressure in the left auricle rises at approximately the same rate as the pressure on the right side of the heart. This is what we should expect, since increased pressure in the inferior vena cava causes increased filling of the right heart and therefore increased output. The whole of this output is driven into the left auricle, so here again there must be a direct connection between venous pressure, diastolic filling and output. When, however, the demands on the functional capacity of the heart are increased by increasing the inflow into the right side of the heart to a maximum, marked differences may be found between the pressures in the right and left auricles, and these differences are especially pronounced when the heart fails or is on the point of failing. They are due to the fact that failure may commence on one side of the heart before the

TABLE III. *Left auricle.*

EXP. 1. Heart weight 70 gms. Cannulæ in inferior vena cava and left auricle.

Height of venous reservoir (cms.)	Blood pressure	Pulse rate	Output per minute (c.c.)	Pressure in left auricle (mm. H_2O)	Pressure in I. V. C. (mm. H_2O)
11·0	110	135	246	30	40
20·5	118	135	455	34	48
35·5	132	138	576	52	60
45·5	138	138	800	54	68
55·5	152	138	845	108	90
60·5	154	135	900	135	98

EXP. 2. Dog 4·15 kilos. Heart 34 gms.; cannulæ in inferior vena cava and left auricle.

Venous supply					
small	86	174	150	−20	20
+	88	174	430	−15	60
+	90	180	668	10	90
+	96	180	965	56	140
+	100	174	1178	79	160
+	105	177	1400	110	102

EXP. 3. Dog 5·5 kilos. Heart 47·5 gms.; cannulæ in inferior vena cava and left auricle.

moderate	86	186	690	40	30
+	92	186	2000	240	200
full	90	180	2100	400	260
−	90	180	1500	600	330

EXP. 4. Dog 7·2 kilos. Heart 60 gms.; cannulæ in inferior vena cava and left auricle.

moderate	94	200	684	2	78
+	90	200	1075	20	106
+	92	200	1980	55	152
full	92	200	2000	54	200
−	92	200	1760	55	210
−	90	192	780	0	64
+	90	192	1500	30	164
full	92	192	1880	54	204

EXP. 5. Dog 5·15 kilos. Heart 44·5 gms.; cannulæ in innominate artery, inferior vena cava, and left auricle; cardiometer.

small	92	192	312	0	54
+	92	186	600	12	67
+	94	186	912	38	84
+	96	186	1250	54	100
+	64	186	2400	80	120
+	66	180	2580	90	132
full	68	174	2460	108	132
−	88	156	6684	36	68

other, and that as a rule the side on which failure commences will be determined by the stress which is laid on it. Thus in the first experiment, with the not excessive output of 900 c.c. per minute for a heart of 70 gms., the pressure in the inferior vena cava was 98 mm. H_2O, while that in the left auricle rose to 135 mm. H_2O. In this case the arterial pressure, against which the left ventricle had to contract and drive out its blood, was 154 mm. Hg.—a high figure for a dog. The residual blood at the end of each systole in this case would be considerable, and the right heart had therefore to get up a pressure on the left side of the heart which would produce sufficient distension over and above the blood remaining in the left ventricle at the end of each systole.

In the third experiment, when the clip on the venous supply was opened to its maximum, the small heart of 47 gms. was evidently unable to deal effectively with the great volume of blood supplied to it. The failure here, however, affected the left side before the right; while the left side was passing out 200 c.c. of blood per minute, the pressure in the inferior vena cava was 260 mm. H_2O, while that in the left auricle was 400 mm. H_2O, *i.e.* higher than the height of the venous reservoir. In this case the pressure in the left auricle was directly due to the strongly contracting right ventricle, the left auricle being so to speak between two fires, the inadequately contracting left ventricle in front, and the strongly contracting right ventricle behind. When shortly afterwards the heart began to fail still more, so that it only sent out 1500 c.c. in the minute and the pressure on the right side rose to 330 mm. H_2O, the pressure in the left auricle rose to 600 mm. H_2O. On the other hand, conditions may arise which put a special strain on the right side of the heart. When the heart in the heart-lung preparation is made to work at its maximum efficiency, there is always a tendency to the occurrence of pulmonary œdema, and in such a case a resistance is offered to the flow of blood through the lungs and so to the contraction of the right side of the heart. In Exp. 4 it is evident that the right side of the heart was not so effective in sending on the blood as the left side was, so that the pressures in the left auricle throughout are much smaller than those in the inferior vena cava. The heart of 60 gms. could only put out 2000 c.c. of blood per minute with a maximal inflow, although the pressure in the right auricle rose to 200 mm. H_2O. The low figure of 54 mm. in the left auricle shows that the left ventricle was able easily to deal with the blood which the right ventricle could send on to it.

The last experiment quoted (Exp. 5) may be regarded as representing

a heart in good condition. It will be noted that here the venous pressures[1] on the two sides rise proportionately with increasing inflow and diminish again proportionally as the inflow is diminished by screwing up the clip on the venous supply tube. It is therefore especially valuable in showing that the significance of rise of venous pressure in producing filling of the heart during diastole, which we have already discussed, applies to both sides of the heart. In a healthy heart which is contracting efficiently, a rise of pressure in the inferior vena cava may be interpreted as indicating a corresponding rise of pressure on the left side of the heart.

4. *The maximum functional capacity of the heart.*

As mentioned at the beginning of this paper, considerable doubt has existed, and still exists, as to the capacity of the heart to vary its output to an extent sufficient to provide for the respiratory needs of an animal during severe muscular exercise, so that recourse has been had to the theory, first put forward by Bohr and Henriques, that a considerable proportion of the oxidative processes of the body may occur in the blood as it passes through the lungs. Experiments by Evans and one of us have shown that there is no foundation for the ascription of such a function to the lungs, and that even the blood from an asphyxiated animal in passing through the lungs takes up only enough oxygen to saturate its hæmoglobin. In a paper published since the appearance of ours on this subject, Henriques, as a result of independent experiments, has come to the same conclusion. The conclusion necessarily follows that in severe muscular work the amount of blood put out by the heart

[1] In all readings of venous pressure, whether on the right or left side of the heart, too much stress must not be laid on the absolute value of the reading. The opening of the inferior cava cannula was at the heart end of the inferior vena cava and therefore at the bottom of the chest cavity with the dog lying on its back. The left auricle cannula was tied into the left auricular appendage, and its orifice was therefore from 3—5 cms. higher than the orifice of the inferior vena cava cannula. The line of zero pressure of the cannula in the inferior vena cava was determined by cutting away the right auricular appendage at the end of the experiment. The registered pressure in this manometer gave therefore a fair idea of the pressure ruling in the part of the heart's cavity near its upper surface. The zero line of the cannula in the left auricle was taken as equal to that in the inferior cava. There may, therefore, be an error of 1 or 2 centimetres in the zero reading. On the other hand the conditions of the experiment would tend to give a higher reading in the inferior vena cava, since the flow into this vessel from the venous reservoir was continuous, whereas the left side of the heart was fed intermittently by the contraction of the right heart, and the main flow into the left side would occur during diastole, when the relaxed ventricle offered no, or a trifling, resistance to the inflow of blood.

and passing through the lungs must be increased five or six fold to carry the increased supply of oxygen which is taken in through the lungs under these conditions. The heart-lung preparation will obviously give us no information as to the amount of blood which can be regarded as normal for that heart in the animal at rest. In fact, such a figure is very difficult to obtain directly. It is quite true that we can expose the heart in an anæsthetised animal and determine by means of a cardiometer the changes of volume at each beat. The conditions of the experiment are, however, so abnormal that it is difficult to say what condition of the normal unanæsthetised animal would correspond with and give the same results as our experiments. The results obtained from the heart-lung preparation may serve, however, as a criterion of the reliability of the results on the output of the heart obtained by indirect methods, such as those employed by Krogh in man. In the heart-lung preparation the minimum output may be reduced, maintaining a normal arterial pressure, until the blood put out is only just sufficient to supply the flow through the coronary vessels, so that we can learn nothing from our preparation as to the minimum output of the heart in its normal relationships. We can, however, learn what is the maximum performance of a heart of any given size. A large number of determinations of the maximum output have been made. In the following table are given the results of nine of these on different animals. In many cases the maximum output was determined only towards the end of the experiment

TABLE IV.

No. of exp.	Weight of dog (kilos)	Weight of heart (gms.)	Arterial B.P.	Pressure I. V. C.	Pressure left auricle	Output per min.	Pulse rate per min.	Output per beat
1	5·3	40	104	170	—	1570	156	10·05
2		82 after adr.	132	45	—	2000	210	9·50
3	6·3	49·5 negative pressure on heart	110	45	—	1720	174	9·85 before adr.
			120	−20	—	1880	227	8·45 after adr.
			140	20	—	2000	222	9·00 more adr.
4	7·2	60	92	156	55	2000	204	9·85
5	5·5	47·5	72	260	400	2100	180	11·90
6	5·75	52	90	66	—	1715	114	15·00
			88	21	—	1715	162	10·2
7	6·45	44	112	76	—	2000	144	13·90
		later	112	130	—	2000	144	13·90
8	5·0	42	—	122	—	2400	180	14·3
9	5·1	56	90	250	—	3000	135	22·3

when the heart was already beginning to suffer from fatigue. The best result we have obtained is that given in Exp. 9. Here, a heart of 56 gms., *i.e.* about one sixth the weight of a human heart, put out for a considerable time three litres of blood per minute against a mean arterial pressure of 90 mm. Hg. and with a pulse rate of 135 per minute and an output at each beat of 22·3 c.c.

If we may take the output of a heart as proportional to its weight, a human heart under the same conditions would put out about 18 litres per minute, which is almost the same as the maximum output obtained by Krogh in his experiments on an athletic man[1]. There seems, therefore, no reason to doubt the conclusions of Zuntz, Plesch, and Krogh, that the extra amount of oxygen taken in during exercise is carried to the tissues by means of a proportional increase in the output of blood through the heart and in the flow of blood through the lungs. The whole question is one of venous inflow. Given sufficient variations of inflow, the heart can vary its output both per minute and at each beat within very wide limits. The circulatory problem in muscular exercise is not therefore how the heart drives the blood round, but the mechanism by which the blood is brought up rapidly from the peripheral parts of the body and driven at a high rate and appreciable pressure into the big veins of the thorax. The blood which comes to the heart will, until the heart suffers from fatigue, be thrown out by this organ.

It may be interesting to compare with these results those of two experiments in which we attempted to obtain some measure of the maximum efficiency of the heart in the whole animal. In these animals, which were anæsthetised in one case by urethane and in the other case by destruction of the brain, the output of the heart was determined by enclosing it in the cardiometer and measuring the excursions of the piston recorder connected therewith. In order to increase the venous inflow, normal saline fluid or blood was allowed to flow into the femoral vein so as to produce a plethoric condition. It will be observed that the highest output per minute obtained in these experiments was 1620 c.c. Under these conditions it is impossible to provide a sufficient venous flow, such as we can supply in the heart-lung preparation, or as in the normal animal is effected by the contractions of the muscles of the abdomen and limbs and the respiratory movements of the thorax.

[1] On the basis of the performance of the heart of 42 gms. in Exp. 8 the corresponding output of a heart of 300 gms. would be 17·1 litres per minute.

TABLE V.

1. *Urethane.*

Weight of dog (kilos.)	Weight of heart (gms.)	Arterial B.P.	Pressure I. V. C.	Pressure left artery	Output per min.	Pulse rate per min.	Output per beat
5·5	40	—	—	90	1620	220	7·40
Saline run into femoral vein. Abdomen pressed.		—	—	45	1500	213	7·05
2. *Decerebrate.*							
4·95	68·5	155	50	30	810	135	6·00
Blood infused into femoral vein.		—	75	210	1500	188	8·00
Salt solution in femoral vein after adrenalin.		144	85	290	1620	220	7·50

CONCLUSIONS.

1. The output of the heart is equal to and determined by the amount of blood flowing into the heart, and may be increased or diminished within very wide limits according to the inflow.

2. The maximum output of the heart may amount to as much as three litres per minute for a heart of 56 gms. The maximum performance of the heart in the heart-lung preparation may therefore correspond with the maximum output observed by Krogh in man during severe muscular work.

3. With a minimal inflow the venous pressure on the two sides of the heart may be zero, and with increasing inflow rises at first only slightly, so long as the amount of blood flowing in is not more than sufficient to exert a minimal distension on the relaxing ventricles.

4. With further increase in the inflow, the venous pressure may be positive throughout diastole, causing an active distension of the heart and an increase in the rate of filling.

5. The maximum venous pressure induced by rise of inflow which can evoke corresponding increase in filling and output of the ventricles may amount on the right side of the heart to about 200 to 250 mm. H_2O.

6. The greater the arterial resistance, the higher will be the venous pressure for any given inflow.

7. The greater the arterial resistance, the sooner will the inflow attain its optimum, and the output its maximum. The maximum output is therefore higher the lower the arterial resistance, provided that the arterial pressure is high enough to maintain an adequate coronary circulation.

8. If the inflow is maintained constant, alteration of rate of heart beat does not alter the output per minute. Under the same conditions,

increase of pulse rate lowers the venous pressure. If therefore the venous pressure is maintained constant, increased pulse rate increases output (because to maintain the venous pressure constant with rising pulse rate, the inflow must be continually increased).

9. The greater the pulse rate, the larger may be the venous inflow without raising venous pressure beyond the optimum. The *maximum* output therefore increases with increasing rate of heart beat.

10. The optimum venous pressure is the amount necessary to produce "maximal" dilatation of the heart during the period of diastole. The maximum size of the heart depends on its structural arrangements, and in the intact animal is determined by the pericardium. It probably represents the size beyond which the heart could not dilate without causing its muscle fibres to act at considerable mechanical disadvantage in raising intracardiac pressure.

11. With a constant inflow, fatigue of the heart is shown by a rise of venous pressure accompanied by increased diastolic filling and mean volume of the heart, the outflow remaining constant.

12. The above statements as to venous pressure apply to both sides of the heart. When failure occurs under a maximal load, either the right or the left side of the heart may fail before the other side.

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